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STERNE, KESSLER, GOLDSTEIN & FOX PLLC 1100 NEW YORK AVENUE, N.W. WASHINGTON, DC 20005				
			EXAMINER TON, THAIAN N	
			ART UNIT 1632	PAPER NUMBER

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/080,713	Applicant(s) COLMAN ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 July 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 62-67,70-73,75-90,98-100,102-127 and 131-133 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 62-67,70-73,75-90,98-100,102-127 and 131-133 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7/25/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/25/05 has been entered.

Applicants' Amendment and Response, 7/25/05, has been entered. Claims 62, 73, 90, 105, 131-133 are amended; claims 91-97 and 128-130 are cancelled; claims 62-67, 70-73, 75-90, 98-100, 102-127, 131-133 are pending and under current examination.

The Ayares Declaration, filed 7/25/05, has been considered.

Information Disclosure Statement

Applicants' Supplemental IDS, filed 7/25/05, has been considered and made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62-67, 70-73, 75-90, 98-100, 102-127, 131-133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants have now amended the claims to recite that the somatic cell used in the nuclear transfer (NT) methods has a normal karyotype, and that the Ayares Declaration clearly shows that the general technique of NT is well-known, thus, when using a new donor cell type for somatic cell NT, the worker simply has to recognize that it is a "numbers game" and one must repeat the experiment using well-known techniques until success is achieved. Dr. Ayares establishes that it can routinely require hundreds or thousands of embryo transfer to produce a viable cloned animal, which can take as little as two weeks to perform on a routine basis. Thus, Applicants are arguing that NT, as a methodology, is well-known, and would not require undue experimentation to practice the claimed invention. See p. 11, 1st paragraph.

Oback et al. Applicants and the Ayares Declaration argue that this paper reports false negative results in presenting data that some somatic cells have a 0% cloning efficiency. Table 1, which reports the cloning efficiency of fibroblast cells, reports a cloning efficiency for fibroblasts of between 0.05% and 1.2%, and a cloning of 0.05% represents 1 viable clone per 2000 embryos transferred (*emphasis in original*). Ayares Declaration argues that when Oback presented the data in Table 1, the actual numbers of embryos transferred, and that the primary references (from which these numbers were calculated) were analyzed to determine the actual number of embryos that were transferred for each cell type that Oback reported a cloning efficiency to be zero. Applicants argue that of the 5 somatic cell types reports by Oback to have a 0% cloning efficiency (mature sertoli cells, lymphocytes

from the thymus, macrophages from the peritoneal cavity, leukocytes from the spleen and neuron/glia from the brain) have been since used to produce cloned animals. See p. 11 of the Response.

On a preliminary note, the Examiner notes that the cited references that have since been used to produce cloned animals are not found to be enabling, because an invention must be enabling at the time of filing. See MPEP § 2164. Thus, the production of cloned animals, after the instant application's filing date, is not considering enabling, because the enablement of the invention is determined at the time of filing. Applicants arguments, in short, are based upon analysis of Oback *et al.*, and concluding that the only limiting factor in successful NT (to produce a live offspring) is found to be in the number of embryos transferred. Thus, the Ayares Declaration and Applicants' arguments state that the sample numbers are too small to drawn any conclusion on the "clonability" of the cell types provided in Oback *et al.* See also, #13-21 of the Declaration. The Declaration and Applicants' arguments set forth that NT is a well-known technology, and that any somatic cell can be reprogrammed using these methods. Furthermore, these arguments imply that it would not require undue experimentation to practice the claimed invention, and that one of skill in the art would only have to do simple manipulations of this technique in order to arrive at viable offspring.

These arguments are not found to be persuasive. Nuclear transfer, as a method, may be well known, but determination of the state of the art at the time of filing, and consideration of the working examples in the specification, provide sufficient evidence that this technology is exceedingly unpredictable with regard to what cell types to use as donors, particular oocytes (for example MII or telophase II), and the subsequent activation, and further development of the NT unit to form a live born offspring. The prior art, for example Fulka (cited on pp. 4-5) of the Office action mailed 4/21/04, support this unpredictability, as they recognized that the cloning of animals required a process, whereby the donor nucleic, by a mechanism

that was unclear, was reprogrammed such that the differentiation state of the donor nuclei returned to totipotent. Oback support this by showing that we do not know what makes a good donor cell, and that the cells tested repeatedly fail to generate viable offspring (see p. 147). Oback clearly teach that it is not merely the donor cell type that is a factor in determining successful NT, but genetic differences between donors (including mitochondrial heteroplasmy, epigenetic differences between donor cells), the effect of the donor cell cycle on the outcome of NT. Overall, Oback present the argument that it is not simply a matter of choosing a particular donor cell, but that various factors, which are art-recognized, play significant roles in the unpredictability of NT. This is further supported by the post-filing art of Campbell *et al.* (Reprod. Dom. Anim., 40: 256-268 (2005)) who review the state of the art of NT, and teach various unpredictable factors, including the inefficiency and low frequency of development to term of NT embryos, as well as various developmental abnormalities observed in the NT derived embryos. See p. 257, Efficiencies and Deficiencies of the Cloning Procedure. With regard to the choice of a particular, suitable donor cell, they teach that although different cultured cells, as well as some somatic cells can be used in NT, there are varying results using these cell types, and they state that, "Unfortunately no conclusion can be made on what is the most appropriate cell type for SCNT." See p. 261, Selection & culture of a suitable donor cell. Tian et al. (Reprod. Bio. & Endocrin., I(98): 1-7 (2003)) also support the unpredictability in selection of an appropriate donor cell, they teach that somatic cells have varying cloning competence and that although specific cell types have found to be successful in producing cloned animals, "A clear consensus, however, has not been reached as to the superior somatic cell type for nuclear transfer." They compared various donor cell types from the same donor animal and conclude that the donor cell type can significantly affect embryo development, both *in vitro* and *in vivo*. See pp. 3-4, Cloning competence of various somatic cell types. Thus, specific guidance must be provided to enable the claimed

invention in view of the unpredictable state of the art with regard to NT in general, and specifically, for the specific donor cell used.

Although Applicants suggest that arriving at successful NT is only a numbers game, there is no specific guidance in the art of record, Applicants' arguments, or the Ayares declaration, which provides sufficient and specific guidance with regard to specific numbers that would be used to enable the invention – which is directed to any somatic cell type. Although the Declaration provides guidance with regard to using endothelial cells, by stating that they transferred 341 embryos and this resulted in the delivery of three healthy piglets with the cloning efficiency of 0.9%, which is within the range reported for other cell types, this does not provide specific guidance for any cell type other than endothelial cells. For example, it is unclear how many nuclear transfer units were produced or how were the 341 embryos selected. Finally, it is reiterated that although NT methodology is well-known to the skilled artisan, taken as a whole, the production of live-born animals using NT is not considered predictable. Although a live-born animal may be generated in specific conditions, or with specific cell types, this does not provide general guidance for the breadth of the claims. A review of post-filing art shows that the unpredictabilities in the NT art have yet to be overcome.

For example, Li *et al.* (Reprod. Bio. & Endocrin., I(84):1-6 (2003)) state that, "[O]verall efficiency of nuclear transfer is still very low and several hurdles remain before the power of this technique is harnessed. Among these hurdles include an incomplete understanding of biologic processes that control epigenetic reprogramming of the donor genome following nuclear transfer. Incomplete epigenetic reprogramming is considered the major cause of the developmental failure of cloned embryos and is frequently associated with the dysregulation of specific genes. At present, little is known about the developmental mechanism of reconstructed embryos. Therefore, screening strategies to design nuclear transfer protocols that will mimic the epigenetic remodeling occurring in normal embryos

and identifying molecular parameters that can assess the developmental potential of pre-implantation embryos are becoming increasingly important.” See Abstract. Li further state that, “The factors involved in the success of NT are very complex. Although many protocols have been modified and utilized in the NT processes, some events continue to remain ill-defined.” See p. 1, last paragraph. This further supports the unpredictability in the art – if it would be routine experimentation to produce cloned animals, then one could expect that any donor cell could be successfully used to produce any species of animal. Such has not been found to be the case. Li *et al.* teach, “The low efficiency and abnormal development of cloned animals are mainly due to incomplete reprogramming and abnormal gene expression.” See p. 2, 1st column, 2nd full ¶. They further state, “[M]ost cloned embryos have been observed to fail to develop to term, and some of the surviving cloned animals have shown abnormalities. The major cause may reside in faulty or incomplete epigenetic reprogramming of the donor nucleus, which affects the gene expression needed for every developmental stage of cloned embryos and offspring. Most cloned embryos lose their developmental abilities during pre-implantation and gastrulation. Moreover, the surviving adults often show abnormalities.” See p. 2, col. 1-2, bridging ¶. McEvoy *et al.* (Reprod. Supp., 61 :167-182 (2003)) support this unpredictability, citing that the production of NT-derived ruminants is an inefficient process that generally fails to generate viable offspring. They suggest that after NT, fetal losses are due to significant developmental retardation and placental inadequacies, and state the following, “Indeed, the fact that losses can occur at all stages and in various guises, ranging from gross degeneration of preimplantation embryos to sudden post-natal death of apparently normal offspring, confirms that NT procedures are frequently responsible for fundamental and far-reaching disruption of developmental norms. Intuitively, it could hardly be otherwise, given that the reconstructed egg comprises a severely traumatized host cytoplasm fused to a donor cell (or nucleus) with which, to a greater or lesser extent,

depending on its origin, it is virtually incompatible from the outset. Therefore, the more remarkable phenomenon is that, against the odds, NT sometimes results in the generation of viable offspring." (Emphasis added, p. 173, Nuclear Transfer Technology, paragraphs 2-3). Therefore, NT transfer is clearly not a method that only requires routine experimentation in order to practice, but a complex method that is unpredictable at various stages, as evidenced by the cited art.

Applicants' arguments regarding NT success rates as a mere "numbers game" is not found to be persuasive. It is clear that the art recognizes that other factors – including incomplete reprogramming, developmental and placental abnormalities – play key roles in determining embryo viability. The increase in number of embryos would not address this issue, as this is not linked to the numbers of embryos, indeed, it would appear from the state of the art, that although it would be possible to produce an NT embryo, the further development of this embryo would be considered exceptionally unpredictable. This is further supported by McEvoy *et al.* (Reproduction, 122:507-518 (2001)) who state that large offspring syndrome (LOS) which occurs in cloned animals, demonstrates that the manipulation of the environment of an embryo can alter subsequent fetal, placental, and pre-and post-natal development profoundly. See p. 507, 1st column, last paragraph. The impact of the *in vitro* environment in which the embryo is cultured significantly affects the subsequent development of the embryo. With specific regard to NT, McEnvoy state the following, "Nuclear transfer is not a robust technology in either murine or domestic animal studies and most reconstituted eggs never generate viable offspring. ... Consequently, it may be unreasonable to expect a high survival rate, but it remains to be seen whether the efficiency of generating viable blastocysts, fetuses and offspring can be improved significantly. As progression from the time of nuclear transfer to the birth of resultant offspring is a multi-stage process, it is difficult to predict how efficiently mouse, cattle or sheep clones can be produced. For example, sometimes only a selected cohort of surviving embryos is transferred

... with the possibility of the outcome thereby exaggerating the overall efficiency relative to studies in which all surviving embryos are transferred.” See p. 512, 2nd column, Nuclear transfer – lessons and limitations. They further state that, “Evidence from most nuclear transfer studies indicates that losses during pregnancy and at or soon after birth are considerable, with a range of abnormalities contributing to this wastage.” See pp. 512-513, bridging sentence. They state that, “One factor that influences the efficiency of nuclear transfer and normality of resultant offspring is the choice of cells for provision of donor nucleic. Renard (1998) noted that late abortions and neonatal deaths in cattle were more frequent after nuclear transfer of somatic nucleic after nuclear transfer of embryonic nucleic, indicating that karyoplast origin may influence the extent of deviant development in clones. In choosing cells for cloning of domestic animals or mice, decisions may be constrained by end-use considerations as much as the resilience or age of potential donor cells.” See p. 513, 2nd column, last ¶.

Thus, it is clear from a review of post-filing art that it is not simply an increase in the numbers of embryos that lead to a proportional increase in live offspring. The method of NT, in and of itself, may be well-known, but the factors that contribute to the generation of live offspring is far from predictable. Accordingly, it is maintained that the claimed invention is not found to be enabling for the breadth of the claims, which recite using any recipient somatic cell, with a normal karyotype, in order to produce a transgenic animal.

The breadth of the claims is directed to a transgenic animal. The term “animal” encompasses a large number of species, such as amphibian, birds, and insects. However, the specification provides no guidance or teachings with regard to production of any animal using NT methodology. For example, Sang (Cloning & Stem cells, 4(3):289, Abstract only) who review the state of the art of NT in birds, they clearly state that the process has not been fully developed, and that the early development of the amphibian embryo would be more useful than the methodologies

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used in mammals, further, they teach the various unpredictabilities involved in, for example, isolation and manipulation of avian oocytes or zygotes. Neither the guidance from the specification, working examples, nor state of the art provide specific guidance with regard to the breadth of the claims, which encompass NT in any animal. The state of the art clearly shows the unpredictability in the art with regard to other animal species, and thus, it would require undue experimentation for one of skill in the art to practice the instantly claimed invention.

Homologous Recombination. Applicants and the Ayares Declaration argue that homologous recombination is a natural event that occurs in all cells, and that all cells are capable of successfully undergoing homologous recombination, because it is an essential mechanism required for all viable cells. As pointed out in the Declaration, the issue was raised regarding whether cells other than fibroblasts could be targeted, since other cell types may not have equivalent proliferative potential. As discussed, Applicants argue that it was feasible, as of the filing date of the present application, to obtain and screen for homologous recombination in cell types that do not have a high proliferative potential, and Applicants point to Zimmer and Gruss, and Jasin *et al.* Particularly, Zimmer & Gruss teach using PCR to screen for homologous recombination events in mouse ES cells, and Jasin *et al.* teach the use of FACS in order to rapidly detect homologous recombination events in transfected cells. Therefore, Applicants argue that as early as 1989, several methods, including PCR-based and FACS-based techniques, were known to those skilled in the art in order to detect targeted integration events after homologous recombination within 3-5 days. See #22-28 of the Declaration and page 12 of Applicants' Response.

Both references, and Applicants' arguments and Declaration have been considered, but are not persuasive. Although homologous recombination may be an essential event in all cells, this does not provide guidance with regard to the targeting of a particular homologous recombination event, and the subsequent

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selection of a particular cell. The issue at hand is directed towards the ability for one of skill in the art to specifically target a particular gene, in the genome of a somatic cell, and modify this particular gene, and then identify and select recombinant cells. The art provided in prior Office actions shows that the working examples in the specification are directed to specific cell types (fetal fibroblasts, and primary mammary epithelial cells). As stated previously, Thomson shows that premature senescence often occurs in gene targeted cells, which makes it difficult to confirm a targeting event in somatic cells, and this is supported further by Polejaeva & Campbell (cited previously) who show that specific guidance must be provided in order to enable specific cell types in gene targeting, and subsequent NT methods. The Zimmer & Guss reference is not within the scope of this argument; this reference is directed to homologous recombination in ES cells, not a somatic cell. Although it is well-known in the art to target mouse ES cells by homologous recombination, this is not the instant invention, which is directed to specific targeting of a somatic cell. Thus, although one of skill could verify a gene targeting event by PCR, the teachings of Zimmer & Guss provide no guidance with regard to the specific targeting of a somatic cell. The Jasin *et al.* reference has been considered, but is not found to be persuasive. Firstly, the claims encompass any somatic cell, this includes primary somatic cells. However, Jasin *et al.* do not discuss the use of a primary somatic cell, they use a cultured COS-1 cell. Specific embodiments of the claims are directed to using primary somatic cells for use in NT methods. See, for example, claims 86, 117. At the time of filing, one of skill in the art would have had to use undue experimentation to practice the breadth of the claimed invention. Applicants assert in the Response, filed 7/14/04, that this invention shows unexpected results, relative to those available at the time of filing, particularly, "[T]he present application demonstrates for the first time that, contrary to previous teachings, a primary somatic cell can be modified *in vitro* by gene targeting and can subsequently support successful nuclear transfer to produce

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a healthy animal. Reasons why this would have been a surprising (*i.e.*, nonobvious) finding including: targeting in primary cells, as opposed to immortalized cells, was *previously thought to be impractical* because the expected low frequency of homologous recombination meant that it would be necessary to transfect and screen large cell populations." Applicants further state that, regarding the claimed invention, that "Thus, it is clear that the present invention provides results that were not expected in view of knowledge available in the art as of the filing date of the present application." See pages 22-23 of the Response, filed 7/14/04. Applicants have clearly stated, on the record, that the results obtained in their invention, would not be expected (*i.e.*, predictable) in view of the state of the art at the time of filing. Thus, given these statements, and the state of the art, provided previously, it is maintained that although homologous recombination does occur in all cells, the targeting of a specific gene, in a specific cell type, is found to be generally unpredictable. Accordingly, it would have required undue experimentation for one of ordinary skill in the art to practice the claimed invention.

The state of the art of donor cell technology is such that it would not be predictable that any somatic cell could successfully be modified, and further, that a resulting genetically modified somatic cell could then be successfully used in NT methodology to produce a live transgenic animal. Thus, specific guidance must be provided by the specification to enable the claimed invention. Although Applicants have provided specific working examples with regard to gene targeting in ovine fetal fibroblasts (see Examples 1 and 3), porcine fetal fibroblasts (Example 6) and primary bovine fetal fibroblasts (example 7) and ovine mammary epithelial cells (example 5), the specification fails to provide sufficient guidance to show that these gene targeted cells result in live born animals in a predictable manner. The specification teaches the generations of live born lambs using primary ovine fibroblasts (examples 1 and 3) but do not provide any working examples with regard to the other recited cell types from other species. It is reiterated that the breadth of

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the claims is directed to any somatic cell type which must first be able to be genetically modified at a specific endogenous locus, and then the resulting transgenic somatic cell must then be used in a NT method to produce a non-human transgenic animal. The state of the art clearly shows that these steps are unpredictable with regard to the specific somatic cell that is to be used, and the further development of the NT unit to form an embryo and then develop to term. Note further that specific embodiments of the claimed invention are directed to specific animals (such as sheep, cow, bull, goat, pig, horse, camel, rabbit or rodent, see, for example, claim 63). This is not found to be enabling for the reasons cited previously and specifically because the specification fails to provide specific teachings with regard to the generation of these transgenic animals, for example, the particular somatic cell to be used as a donor cell. The state of the art clearly teaches that the donor cells to be used in somatic NT methods are neither predictable nor routine for different species (see above), and the specification fails to overcome this art-recognized unpredictability. Furthermore, specific embodiments of the claims are directed to producing transgenic offspring from the resulting transgenic animals. The specification fails to provide an enabling disclosure for these embodiments because there are no specific teachings which overcome the art's unpredictability with regard to the generation of viable offspring.

Recipient Cells. Applicants have now amended the claims to recite that the recipient cells are oocytes, two-cell embryos or zygotes. See p. 13 of the Response. This has not overcome the prior rejection. Although these cell types are found to be able to produce viable offspring in the art, the prior Office actions clearly show that the particular oocytes (MI, MII and telophase) have found to be enabled by the art, however, the claims are broader than this, as they recite any oocyte. Finally, it is reiterated that the claims do not recite that the recipient oocyte/two-celled embryo or zygote is enucleate. As stated previously, if the recipient cell is not enucleate the embryo would be tetraploid.

Species/Genus. Applicants clarify that the claims are limited to transferring the embryo to a surrogate mother that is able to carry the embryo to term, and thus, the term "species" is meant to describe only animals within a taxonomic genus. See p. 13 of the Response. Although Applicants have stated this, the claims are broad and encompass producing a live born by any means, means which are not specifically disclosed in the instant specification. Thus, it is suggested that Applicants amend the claims to clarify that the NT unit, embryo and surrogate mother are of the same species, in order to enable the claim.

Abundant Expression. Applicants' amendments to the claims, which no longer recite "abundant expression" renders the prior rejection with regard to this aspect, moot. See p. 13 of the Response. However, it is maintained that there is no guidance as to what locus, other than the exemplified collagen locus, which would provide the claimed 1:100 gene targeted cell:randomly targeted cell clone ratio. It is further maintained that the specification fails to provide guidance as to other means of genetic targeting, other than homologous recombination. The working example provided by the instant specification is by preparation of a vector for homologous recombination, and without further teachings with regard to the characteristics that of abundant expression of a particular endogenous gene locus, or what would make a gene targeting event result in a gene target cell:randomly targeted cell clone ratio of equal to or greater than 1:100, the specification fails to enable the breadth of the claims.

Genotype/Phenotype. Applicants argue that the modification of a genome of an animal by means of a genetic targeting event creates an animal that allows the expression of a desired protein, or disruption of a gene expression an undesired protein. Applicants argue that, therefore, the transgenic animals will not always display the genetic changes, but may only reveal the modifications upon expression or lack of expression of the targeted gene, and that scientists are able to identify

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animals with modified genomes using routine techniques, such as PCR. See pp. 13-14 of the Response.

These arguments are not persuasive. Specific embodiments of the claims are directed to targeting using a specific promoter, see claims 70-73, 102-105, for example. The claimed embodiments are directed to placing a promoter adjacent to an endogenous gene in the nuclear genome, wherein the promoter is the collagen gene promoter, or a milk protein gene promoter. Although one of skill in the art may be able to identify a transgenic animal, one could not predict what phenotype this animal would exhibit. Thus, without a particular phenotype, there is no enabled use of the particular animal. Applicants have not provided specific guidance with regard to the embodiments that encompass these specific genetic modifications, and one of skill would not be able to rely upon the art to predict the phenotype of the resultant animal. The prior Office actions have provided evidence for this unpredictability (see, for example, Kappell, Mullins, Mullins, Houdebine, Wall, Cameron, Sigmund, and Niemann, cited in the Office action mailed 4/21/04, particularly, pages 12-14). The instant claims are not enabling because they claim transgenic animals which do not have an apparent phenotype, and thus, one of skill would not know how to use these animals. Thus, it is maintained that the specification fails to provide specific guidance for the breadth of producing any transgenic non-human animal whose genome comprises a modification at an endogenous locus by a gene targeting event, and thus, it would have required undue experimentation to predict the results achieved in any one hose animal comprising and expressing a particular transgene, the levels of the transgene product, the consequences of that product, and the resulting phenotype.

Accordingly, for the reasons cited above, it would have required undue experimentation for the skilled artisan to carry out the claimed methods, with a predictable degree of success, to implement the invention as claimed.

Claim Rejections - 35 USC § 112

The prior rejections of claims 90,97-127 and 133 are rendered moot in view of Applicants' amendments to the claims.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tnt

Thaian N. Ton
Patent Examiner
Group 1632



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PRIMARY EXAMINER